

**REMARKS/ARGUMENTS**

With this amendment, claims 34-39, 43, 64, 65, 74, and 113-128 are pending in the application. Reconsideration of the claims in light of the following remarks is respectfully requested.

**I. Status of the Claims**

Claims 34, 37, and 38 have been amended. These amendments add no new matter. Support for the amendments can be found in the original specification, *e.g.*, at paragraphs [0017], [0053]-[0056], [0084], [0211]-[0218], and [0237]-[0248].

Claims 64 and 65 have been amended. These amendments add no new matter. Support for the amendments can be found in the original specification, *e.g.*, at paragraphs [0084], [0211]-[0218] and [0237]-[0248].

Claim 74 has been amended. These amendments add no new matter. Support for the amendments can be found in the original specification, *e.g.*, at paragraphs [0084], [0211]-[0218] and [0237]-[0248].

New claims 113-128 have been added. These new claims add no new matter. Support for the new claims can be found in the original specification, *e.g.*, at paragraphs [0053]-[0056], [0101]-[0119], [0211]-[0218] and [0237]-[0248].

Claims 1-33, 40-42, 44-63, 66-73, and 75-112 have been canceled without prejudice. Applicants reserve the right to prosecute the claimed subject matter in a related, co-pending application.

## **II. Objection to Claim 37**

Claim 37 stands objected to because the Examiner believes that the abbreviations “AEB,” “AEVB,” “MMAF,” “MMAE,” and “AFP” are unclear. The Examiner is aware that abbreviations can be used in a claim, but the Examiner submits that the first recitation of the abbreviation should be preceded by the full terminology.

Applicants respectfully disagree with the objection and point the Examiner, for example, to paragraphs [0053]-[0056] in which each of the abbreviations is defined. Nevertheless, claim 37 has been amended per the Examiner’s suggestion. Applicants respectfully request removal of the objection.

## **III. Objections to the Disclosure**

The Examiner has objected to the disclosure, asserting that fonts in paragraphs [0109], [0110], [0111], [0112], and [0113] need to be corrected.

Upon review of the PCT Application WO 2005/084390 corresponding to the present application, Applicants note possible scanning distortions of the text and assume these distortions are the subject of the objection. As set forth above in the “Amendments to the Specification,” paragraphs [0109]-[0113] have been replaced with properly formatted paragraphs to address the Examiner’s objection.

In view of the comments above, Applicants respectfully request removal of the objection.

## **IV. Rejection of Claims 34-39, 43, 64-65 and 74 under 35 U.S.C. § 112, first paragraph**

Claims 34-39, 43, 64-65 and 74 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was allegedly not suitably described in the specification. In particular, Applicants interpret the Examiner’s rejection to be based primarily on the assertion that at the time of filing, applicants were allegedly not in possession of a method of preparing a conjugate of any protein, such as any antibody, having one or more disulfide bonds and any drug, using any reducing agent; and reoxidizing the undisclosed protein or drug or

antibody with any oxidizing agent. *See* page 5 of the Office Action. Applicants respectfully disagree and traverse below.

As an initial matter, while Applicants do not acquiesce to the Examiner's reasoning regarding whether the specification adequately describes conjugation of protein, currently amended claim 74 is now directed to a method of preparing a mixture of antibody drug conjugates.

In addressing the Examiner's general rejection, Applicants begin by pointing the Examiner to the "Background" section of the specification. As demonstrated by this section, it was known at the time of filing that antibody drug conjugates could be used to deliver active drug to a tumor cell. It was also known that antibody drug conjugates having 8 drugs per antibody could be synthesized by conjugating a drug capable of interacting with reduced thiols to the interchain thiols of a fully reduced antibody. As stated in paragraph [0004], "[t]he common convention for producing ADCs conjugated through the disulfide bonds has been by reducing all inter-chain disulfide bonds of an antibody and reacting all the reduced mAb thiols with a compound capable of interaction with all the reduced thiols, forming uniformly-substituted ADCs with 8 drugs/mAb, i.e. "fully loaded," without the ability to obtain specificity for a certain site of conjugation."

Doronina *et al.* (as cited by the Examiner) further establishes the knowledge in the art at the time of filing the present application. In particular, the reference supports the notion that there was consensus in the art that reducing and conjugating drug to an antibody preserved structure and function across a variety of antibodies. Doronina *et al.* describes on page 779: "The mAbs were reduced and then alkylated with the maleimido-containing MMAE and AEVB drug derivatives, forming nonaggregated conjugates with about eight drugs attached per mAb. This reductive conjugation method preserves mAb affinity, [and] is applicable to many IgGs..." Moreover, on page 782, Doronina *et al.* states: "[t]he results using a variety of IgGs, including cBR96 and cAC10 as reported here, suggest that the chemistry is widely applicable..." And the Examiner on page 5 suggests agreement with this notion, stating that "general knowledge in the art may have allowed one [of] skill in the art to conjugate antibody to a drug..." Applicants submit, however, that while certain conjugation, reduction, and oxidation chemistries were well-

known, the claimed method of conjugation via a full reduction of an antibody, followed by a partial reoxidizing, and a subsequent conjugation was not known.

For at least the reasons listed below, Applicants further submit that the specification provides more than adequate support for the currently pending claims.

First, antibodies were well-known at the time of filing the present case. The specification elaborates on this general knowledge, *e.g.*, by defining “antibody” in paragraph [0046] and citing Harlow & Lane to substantiate well-known characteristics of antibodies. Moreover, the specification provides vast disclosure of specific structural characteristics of antibodies in, *e.g.*, paragraphs [0047]-[0051] and paragraphs [0063]-[0081]; those paragraphs further include citation to several references that provide even more detail regarding well-known antibody structure and function. Moreover, the claims specify that the conjugation is via the interchain thiols of the antibodies.

Second, reducing agents for reducing, *e.g.*, interchain disulfide bonds on antibodies were equally well-known in the art and adequately supported. For example, paragraph [0087] states that: “full reduction of the antibody [can be achieved] with a reducing agent such as *but not limited to* DTT or TCEP. ... Encompassed in the disclosure are hybrids and variations of the above methods which would be known to one of skill in the art.”

Third, oxidizing agents for reoxidizing, *e.g.*, interchain thiols on antibodies were similarly well-known in the art and adequately supported. For example, the specification lists *six non-limiting* oxidizing reagents in paragraph [0087]. As above, paragraph [0087] also states that hybrids and variations would be known to one of skill in the art.

Finally, methods of attaching drugs to antibodies via a maleimide group is known in the art and described in the specification. See, for example, paragraphs [0084], [0129], and the Examples section. The claims, as amended, specify that the conjugation is via a maleimide group.

In view of the comments above, Applicants respectfully request that the rejection to claim 34-39, 43, 64-65 and 74 under 35 U.S.C. § 112, first paragraph be withdrawn.

**V. Rejection of Claim 64 under 35 U.S.C. § 112, second paragraph**

Claim 64 stands rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicants regard as the claimed invention.

Without acquiescing to the Examiner's position, Applicants note that claim 64 has been amended to further clarify the claimed subject matter. Claim 64 now reads in part "contacting an antibody solution with a large excess of a reducing agent and incubating the resulting solution at about 37 °C for about 30 minutes, to produce a fully reduced antibody."

In view of the comments above, Applicants respectfully request that the rejection to claim 64 under 35 U.S.C. § 112, second paragraph be withdrawn.

**VI. Rejection of Claims 34-39, 64-65 and 74 under 35 U.S.C. § 102(a)**

Claims 34-39, 64-65 and 74 stand rejected under 35 U.S.C. § 102(a) as being anticipated by Francisco *et al.* (*Blood* 102(4): 1458-1465, August 2003, PTO 1449) as evidenced by Sears *et al.* (*Proc. Natl. Sci. USA* 72(1): 353-357, January 1975, PTO 892).

The Examiner believes that Francisco *et al.* teach a method of preparing a protein conjugate, such as an antibody conjugate, to a drug, such as cAC10-vcMMAE, wherein the antibody is cAC10 that binds to CD30 having one or more disulfide bonds and the drug is MMAE. Furthermore, the Examiner appears to assert that the methods described in Francisco *et al.* with supporting evidence from Sears *et al.* must function the same as the presently claimed methods. Applicants respectfully disagree and traverse below.

As an initial matter, Applicants respectfully submit that Sears *et al.* was improperly cited as evidence. As indicated by MPEP 2131.01, the use of multiple references for 35 U.S.C. § 102 is very limited. Only three uses for multiple references exist: 1) to prove the primary reference contains enabling disclosure, 2) to explain the meaning of a term, or 3) to show inherency. Sears *et al.* provides none of the uses, and the Examiner cites none of them either. Instead, the Examiner improperly applies a notion that the reference teaches reoxidation of human IgG1 with its four interchain disulfide bonds by simply exposing the antibody to air

and adjusting pH. Francisco *et al.* discloses a starting pH of 8.0, which is not within the range of pH (pH 3.5 to 7.5) cited in Sears *et al.* Thus, for at least these reasons, the reference cannot be used to support the rejection under 35 U.S.C. § 102(a).

Assuming *arguendo* that Sears *et al.* was properly cited, Applicants respectfully traverse the rejection. “A claim is anticipated only if *each and every element* as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.” *Verdegaal Bros. v. Union Oil Co. of Cal.*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987) (emphasis added). Applicants respectfully submit that Francisco *et al.* even with Sears *et al.* as evidence does *not* teach each and every element of the amended claims.

Francisco *et al.* describes the conventional method for producing ADCs referred to in the Background section of the specification. In Francisco *et al.*, the conjugate is prepared by reducing all of the inter-chain disulfide bonds of the antibody and reacting the reduced thiols with drug-linker to arrive at ADCs having 8 drugs per antibody, in other words, fully loaded antibodies. The antibody described in Francisco *et al.* is an IgG1 having a total of 8 interchain thiols when reduced.

This is in contrast to the claimed methods that describe conjugation methods for producing partially loaded antibodies. The claimed methods recite an oxidation step to reform at least one interchain disulfide bond of an antibody prior to conjugation.

As to independent claim 34, Francisco *et al.* even with Sears *et al.* at least fails to teach or suggest addition of any oxidizing agent to a fully reduced antibody, let alone a step of “treating the fully reduced antibody with *limiting amounts of a reoxidizing agent* to reform at least one interchain disulfide bond of the antibody to form a partially reoxidized antibody.” The claim language *limiting amounts*, for example, indicates purposeful action of adding reoxidizing agent to perform the presently claimed method.

As to independent claim 64, Francisco *et al.* even with Sears *et al.* fails to teach or suggest multiple aspects of the claimed method. For example, Francisco *et al.* fails to teach or suggest addition of any oxidizing agent to a fully reduced antibody, let alone “treating the fully reduced and cooled antibody with about 1.5 to about 2.5 molar equivalents of the oxidizing agent to form a reaction solution,” as presently claimed. Moreover, Francisco *et al.* provides no

teaching of "allowing the reaction solution to incubate at about 0 °C for about 10 to 20 minutes and produce a partially reoxidized antibody," as presently claimed.

As to independent claim 74, Francisco *et al.* even with Sears *et al.* fails to teach or suggest multiple aspects of the claimed method. For example, as the Examiner points out on page 7 of the Office Action: "[t]he reference antibody is fully reduced since the drug/antibody ratio of cAC10-vcMMAE is 8:1." Thus, Francisco *et al.* at least fails to teach methods of preparing a mixture of antibody drug conjugates wherein the average number of drugs per antibody in the mixture is less than the number of interchain thiols present on the fully reduced antibodies as presently claimed.

Applicants submit that claims dependent claims 35-39 and 65 will be allowable for at least being dependent from allowable independent claims 34 and 64, respectively.

In view of the amendments to the claims and the claim elements that are not disclosed by the cited art, Applicants respectfully request withdrawal of the rejection of claims 34-39, 64-65 and 74 under 35 U.S.C. § 102(a).

#### **VII. Rejection of Claims 34-39 and 74 under 35 U.S.C. § 102(a)**

Claims 34-39 and 74 stand rejected under 35 U.S.C. § 102(a) as being anticipated by Doronina *et al.* (*Nature Biotech.* 21(7):778-941, July 2003, PTO 892) as evidenced by Sears *et al.* (*Proc. Natl. Sci. USA* 72(1): 353-357, January 1975, PTO 892).

The Examiner believes that Doronina *et al.* teach a method of preparing a protein conjugate, such as an antibody conjugate, to a drug wherein the antibody is cAC10 that binds to CD30 or cBR96 antibody that binds to Lewis Y antigen wherein the antibody has 8 disulfide bonds and the drug is MMAE. Furthermore, the Examiner appears to assert that the methods described in Doronina *et al.* with supporting evidence from Sears *et al.* must function the same as the presently claimed methods. Applicants respectfully disagree and traverse below.

Again, Applicants submit that the Examiner improperly applied Sears *et al.*, as noted above. Also, Doronina *et al.* discloses a starting pH of 8.0, which is not within the range of pH (pH 3.5 to 7.5) cited in Sears *et al.* Thus, for at least these reasons, the reference cannot be used to support the rejection under 35 U.S.C. § 102(a).

Even assuming *arguendo* that Sears *et al.* was properly cited, Applicants respectfully traverse the rejection. Applicants respectfully submit that Doronina *et al.* even with Sears *et al.* as evidence does *not* teach each and every element of the amended claims.

As with Francisco *et al.*, Doronina *et al.* describes the conventional method for producing ADCs referred to in the Background section of the specification. In Doronina *et al.*, the conjugate is prepared by reducing all of the inter-chain disulfide bonds of the antibody and reacting the reduced thiols with drug-linker to arrive at ADCs having 8 drugs per antibody, in other words, fully loaded antibodies.

As to independent claim 34, Doronina *et al.* even with Sears *et al.* at least fails to teach or suggest addition of any oxidizing agent to a fully reduced antibody, let alone a step of “treating the fully reduced antibody with *limiting amounts of a reoxidizing agent* to reform at least one interchain disulfide bond of the antibody to form a partially reoxidized antibody.” The claim language *limiting amounts*, again, indicates purposeful action of adding reoxidizing agent to perform the presently claimed method.

As to independent claim 74, Doronina *et al.* even with Sears *et al.* fails to teach or suggest multiple aspects of the claimed method. For example, Doronina *et al.* describes on page 782, column 1, that mAb-Val-Cit-MMAE had approximately eight drug units per mAb, which corresponds to the “approximately eight SH groups per mAb” as disclosed on page 783 in the “Conjugate Preparation” section. Doronina *et al.* fails to teach partially loaded antibodies with an average number of conjugated drugs *less than* the average number of interchain thiols, as presently recited in claim 74.

Applicants submit that claims dependent claims 35-39 will be allowable for at least being dependent from allowable independent claim 34.

In view of the amendments to the claims and the claim elements that are not disclosed by the cited art, Applicants respectfully request withdrawal of the rejection of claims 34-39 and 74 under 35 U.S.C. § 102(a).

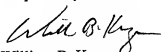
**CONCLUSION**

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

Further, the Commissioner is hereby authorized to charge any additional fees or credit any overpayment in connection with this paper to Deposit Account No. 20-1430.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,



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